Remarks

Claim amendments

Claims 1, 2, 4, 6, 7, 9, 11-14, 16, 18, 20-23, 25, 27, 29-32, 34, 37-41, 43, 44, 46, 48, 49 and 56-71 remain in this application. Claims 1, 2, 4, 6, 9, 11, 13, 14, 16, 18, 20, 22, 23, 25, 29, 31, 32, 34, 37, 40, 41, 43, 44, 46, 49, 57, 57-71 are currently amended. Claims 5, 10, 15, 19, 24, 28, 33, 42 and 45 are presently canceled without prejudice or disclaimer.

Claim 1 is amended to specify that the modified xylanase is a Family 11 xylanase and exhibits improved thermophilicity in comparison to a corresponding native xylanase. Support for this amendment can be found in claim 2 as originally filed and page 5, lines 12 and 13. A similar amendment is made to independent claim 49.

Furthermore, claim 1 is amended by removing reference to the acidic amino acid substitution at position 11. Corresponding amendments are made to claims 18, 31, 40, 57, 59, 68, 70 and 71.

In addition, claim 1 is amended by removing the term "first" from the phrase "first basic amino acid at position 144" and the term "second" from the phrase "second basic amino acid at position 161". Support for this amendment can be found in claim 1 as originally filed, which recites the amino acid substitutions in the alternative. Further support for this amendment is on page 5, lines 7-10. Corresponding amendments are made to claims 4, 9, 13, 14, 22, 23, 31, 32, 40, 41, 44, 59 and 67-71. Claims 9, 14, 58, 60, 69 and 71 are amended to recite the positions of the basic substituted amino acids.

Claims 5, 10, 15, 19, 24, 28, 33, 42, 45 are canceled as they became redundant in view of the amendments to claim 1. The dependencies of claims 6, 11, 16, 20, 25, 29, 34,

43, 46 (which previously depended from these cancelled claims) are adjusted accordingly.

Claims 2, 37, 61 and 63 are amended to remove terms that became redundant in view of the amendments to claim 1.

Claims 13 and 22 are amended to remove the word "further" from the phrase "further comprising".

Claim 60 is amended to remove language that was redundant with respect to claim 59 from which it depends.

Claims 31, 40, 61, 62, 64, 65 and 66 are amended to make minor formality-type amendments.

Duty to Disclose

Examiner requests that Applicant provide a detailed description as to what type of variants have been claimed earlier by the Applicant and whether those patented variants read on any of the variants claimed in the instant application in order to aid the Examiner in his search for Double Patenting issues.

U.S. Patent Nos. 5,405,769, 5,759,840, 5,866,408 and 7,060,482 and Application No. 10/307,441 were previously filed by the Applicant. Application No. 10/307,441 is now abandoned, although a divisional of this application was filed on March 17, 2006.

Descriptions of the subject matter covered by claims of these previous U.S. patents and U.S. patent applications are provided below.

The claimed invention is directed to a modified xylanase having one or more than one substituted amino acid residue selected from a non-polar amino acid at position 116,

a Cys at position 118, a basic amino acid at position 144 and a basic amino acid at position 161. The positions of the amino acid substitutions are determined from sequence alignment with a *Trichoderma reesei* xylanase II enzyme.

The xylanase variants claimed in U.S. Patent Nos. 5,405,769, 5,759,840, 5,866,408 and 7,060,482 do not include amino acid substitutions at positions 116, 118, 144 or 161 as in the instant application.

U.S. Patent No. 5,405,769 (Arase et al.)

Claim 1 relates to a modified family G xylanase having the structure of *B. circulans* or mutated to have essentially this structure. The claim recites amino acid substitutions at positions selected from the group consisting of 100 and 148 or 98 and 152 to form an intramolecular disulfide bridge, or an amino acid substitution at position 179 to form an intermolecular disulfide bridge. An N-terminal mutation is introduced with substitutions of amino acids at positions 3, 4 or 8.

Claim 15 relates to a modified family G xylanase essentially having the structure of the *B. circulans* enzyme or mutated to essentially have this structure. The modified xylanase is selected from clones TS1, TS2, TS3a, TS3, TS4a, TS4, TS4M, TS4D, TS5a, and TS6a, which are described in Table 2, columns 151 to 152. As set out in Table 2, the xylanase mutants contain mutations at the following positions: 3, 4, 8, 98, 100, 148, 152 and 179.

The amino acid numbering in U.S. 5,405,769 is based on alignment with a *B. circulans* amino acid sequence. Mutations at positions 3, 4, 8, 98, 100, 148, 152 and 179 recited in U.S. 5,405,769 correspond to positions 12, 13, 17, 107, 110, 154 and 181 of the

Trichoderma reesei xylanase II sequence. These amino acid positions do not correspond to amino acid positions 116, 118, 144 or 161 of *Trichoderma reesei* II.

Furthermore, none of the dependent claims of U.S. 5,405,769 recite amino acid substitutions at positions 116, 118, 144 or 161 (TrX2 numbering).

U.S. Patent No. 5,759,840 (Sung)

Claim 1 of U.S. Patent No. 5,759,840 is directed to Family 11 xylanases from *Trichoderma*, *Aspergillus*, *Streptomyces*, or *Bacillus* having amino acid substitutions at positions 10 and 14 based on *Trichoderma reesei* xylanase II numbering and having at least 8 amino acid residues in an N-terminus upstream from position 10.

Independent claim 6 relates to Family 11 xylanases of *Trichoderma*, *Aspergillus*, *Streptomyces*, or *Bacillus* and having an amino acid substitution at position 14 based on *Trichoderma reesei* xylanase II numbering and a substitution of amino acids with those of a corresponding aligned sequence of amino acids from *Thermomonospora fusca* xylanase A to form a chimeric xylanase, and an upstream extension of the N-terminus of the chimeric xylanase with the addition of from 0 to 10 amino acids.

Independent claim 17 recites a method of modifying a Family 11 xylanase by (1) substituting wild type amino acids 10, 27 and 29 of *Trichoderma reesei* xylanase II or the corresponding aligned amino acids of another Family 11 xylanase with a different amino acid, (2) replacing a sequence in the N-terminal region with that of corresponding aligned sequences of amino acids from another Family 11 xylanase to form a chimeric xylanase; or (3) adding 1-10 amino acids to the N-terminus of the xylanase.

The positions of the amino acid substitutions in these claims do not correspond to amino acid positions 116, 118, 144 or 161 (*Trichoderma reesei* II numbering).

Furthermore, none of the dependent claims of U.S. 5,405,769 recite amino acid substitutions at positions 116, 118, 144 or 161.

U.S. Patent No. 5,866,408 (Sung)

U.S. 5,866,408 is a divisional of U.S. 5,759,840. The claims of U.S. 5,866,408 are similar to 5,759,840, but are directed to a method of improving the bleachability of wood pulp by treating pulp with xylanases disclosed in U.S. 5,759,840. None of the mutations claimed in U.S. 5,866,408 correspond to the mutations claimed in the present application.

U.S. Patent No. 7,060,482 (Sung and Tolan)

Claim 1 of U.S. Patent No. 7,060,482 relates to a modified Family 11 xylanase comprising at least one intramolecular disulfide bond and a basic amino acid at position 162, and which has at least 40% optimal activity under the conditions specified in the claim.

Dependent claims relate to the following mutants: TrX-162H-DS1, TrX-162H-DS2, TrX-162H-DS4, and TrX-DS8. These xylanase mutants are described in Table 2, column 10 and include amino acid substitutions at positions 10, 27, 29, 44, 108, 110, 125, 129, 158, 162.

The positions of the amino acid substitutions in these claims do not correspond to amino acid positions 116, 118, 144 or 161 (*Trichoderma reesei* II numbering).

Divisional of Application No. 10/307,441 (Serial # not yet received)

A terminal disclaimer is submitted herewith with respect to the divisional of Application No. 10/307,441.

Claim Rejections – 35 USC 112

Scope of claims

Examiner requests clarification from the Applicant with regard to the scope of the claims. Specifically, Examiner is unclear as to whether the modified xylanase is limited to a variant of SEQ ID NO:16, comprising the amino acid substitutions recited in claim 1, or whether the claims are directed to any modified xylanase containing one or more of these amino acids substitutions.

Applicant submits that amended claim 1 relates to any modified Family 11 xylanase comprising one or more than one of the amino acid substitutions specified. As stated in the claim, the positions of the amino acids substitutions are "determined from sequence alignment of said modified xylanase with *Trichoderma reesei* xylanase II amino acid sequence defined in SEQ ID NO:16." It is clear from this language that the modified xylanase is not limited to a *Trichoderma reesei* xylanase II enzyme as defined in SEQ ID NO:16, rather it is the positions of the amino acid substitutions which are determined by alignment with the amino acid sequence of SEQ ID NO:16.

Rejection under USC 112, second paragraph

Examiner rejects claims 5, 10, 15, 19, 24, 28, 33, 37, 42 and 45 under 35 U.S.C. 112, second paragraph, as being indefinite due to the inclusion of the term "derived

from". As set out above, claim 1 is amended to recite that the modified xylanase is a Family 11 xylanase. Since claims 5, 10 15, 19, 24, 28, 33, 42 and 45, which contained the phrase "derived from a Family 11 xylanase", became rendered redundant in view of this amendment, Applicant has canceled these claims. Furthermore, the phrase "and is derived from a Family 11 xylanase" is deleted from claim 37. As a result, Examiner's rejection of these claims is rendered moot.

Rejection under USC 112, first paragraph

(i) Enablement

Examiner rejects claims 1-2, 4-7, 9-16, 18-25, 27-34, 37-46, 48-49, 56-71 under 35 U.S.C.112, first paragraph as lacking enablement. In particular, Examiner alleges that, while the specification is enabling for specific variants of a xylanase corresponding to SEQ ID NO:16, it does not reasonably provide enablement for any modified xylanase comprising a change in any amino acid position and one or more amino acid position selected from the group 10, 11, 27, 29, 75, 105, 116, 118, 125, 129, 144, 161 of SEQ ID NO:16. Examiner states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Amended independent claims 1 and 49 specify that the modified xylanase is a Family 11 xylanase and exhibits improved thermophilicity in comparison to a corresponding native xylanase. Applicant submits that the specification would enable any person skilled in the art to which it pertains to make the invention commensurate in scope with amended claims 1 and 49.

Examiner contends that since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved.

Applicant submits that sufficient guidance is provided in the specification as to which amino acids of Family 11 xylanases would be potentially tolerant of modification. The amino acid sequences of numerous known Family 11 xylanases are provided in Figure 1 and the sequence listing. Figure 1 shows amino acid sequence alignments among Family 11 xylanases. The residues that are conserved or common to all Family 11 xylanases are underlined. It is known to one of skill in the art that the modification of conserved amino acids are less likely to be tolerated by the enzyme, i.e., more likely to result in an inactive or unstable enzyme. A person of skill in the art would avoid making a substitution at a position in the sequence which is conserved and sufficient guidance as to which amino acids are conserved is provided in Figure 1.

Furthermore, claim 1 is amended so that it is now directed to a xylanase with improved thermophilicity in comparison to a corresponding native xylanase. To determine if a modified xylanase displays such improved thermophilicity, and thus would be tolerant of a particular amino acid substitution, would simply require a person of skill in the art to carry out an experiment to determine if the xylanase is more active at a higher temperature when compared to the activity of a corresponding native xylanase when all conditions remain constant (see page 19, lines 14-22). This assay for

determining whether or not an enzyme is thermophilic is described in detail in Example 3.

Examiner alleges that the specification is limited to teaching the use of SEQ ID NO:16 as a parent xylanase wherein amino acids at specific positions such as 10, 11, 27, 29, 75, 105, 116, 118, 125, 129, 144, 161 can be substituted with other amino acids, but provides no guidance with regard to the making of variants and mutants or with regard to other uses comprising modifying any or all amino acids in SEQ ID NO:16. Examiner further states that in view of the great breadth of the claim, the amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. Applicant respectfully disagrees with Examiner's assertion.

Applicant submits that the claims need not be limited to specific exemplified embodiments or technical examples disclosed in the specification. It is only necessary that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. In addition, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims (see MPEP 2164.08).

In the present case, Example 1 describes the construction of various modified xylanases, all of which were found to display enhanced thermophilicity (see Examples 2 and 3). This is sufficient disclosure to satisfy the enablement requirement. Furthermore, many Family 11 xylanases, such as those set forth in Figure 1, have been cloned and sequenced. Provided with guidance from the specification, it would not require undue experimentation for a person of skill in the art to produce a modified Family 11 xylanase

as defined in claim 1 or claim 49 derived from the cloned genes encoding these enzymes. In addition, even if the gene for a given enzyme were not cloned, it is well within the ability of one skilled in the art to clone genes for naturally occurring enzymes. The techniques used to construct the mutant xylanases in Example 1 are basic recombinant DNA methods like plasmid preparation, restriction enzyme digestion, polymerase chain reaction, oligonucleotide phosphorylation, ligation, transformation and DNA hybridization (see page 26, lines 1-5). A person of ordinary skill in the art could easily apply these recombinant methods to produce a modified Family 11 xylanase comprising one or more of the mutations defined in the claims.

Furthermore, Applicant submits that, at the filing date of the present application, it was well within the ability of a person skilled in the art to produce modified enzymes with improved characteristics without necessarily having knowledge of the relationships between the sequence structure and function of the proteins. For example, by employing directed evolution, a modified protein could be constructed without knowledge of the amino acid sequence. This process is known to mimic Darwinian evolution in a test tube combining random mutagenesis and recombination with screening or selection for enzyme variants that have desired properties. It would not have required undue experimentation for one skilled in the art to obtain a Family 11 enzyme with one or more of the mutations recited in claim 1 and perform directed evolution to arrive at a Family 11 xylanase comprising additional mutations that further enhance the thermophilicity of the enzyme or that are compatible with these existing mutations.

Furthermore, if the claims scope is narrowed as suggested by Examiner to that of SEQ ID NO:16, then one of skill in the art upon reading the present specification, may

identify one or more analogous positions within a family 11 xylanase listed in Figure 1, or any other family 11 xylanase, and modify these positions using standard techniques to circumvent the claim. In doing so, the person of skill would not have exercised any inventive ingenuity, yet relied upon the teaching of the specification to arrive at the teaching of the present invention. Clearly the specification provides one of skill in the art a significant amount of information relating to specific, defined, positions within a family 11 xylanase, and sequence comparison of 17 alternate xylanase sequences to ensure that these modifications may be carried in analogous positions in a family 11 xylanase. The limitation suggested by the Examiner would impose an undue burden on the Applicant as one of skill could readily use the teachings of this specification and avoid the narrowed claim scope.

Applicant submits that in view of (i) knowledge of the protein sequences of various Family 11 xylanases and which amino acids are conserved, (ii) the guidance provided in the specification for carrying out an assay to determine if an enzyme is thermophilic, and

(iii) the guidance provided in the specification regarding the preparation of various modified xylanases and the ease in which one of skill in the art could apply known techniques to produce mutated xylanases, the specification would enable any person skilled in the art to make the invention commensurate in scope with amended claim 1 without undue experimentation.

For these reasons, as stated above, Applicant requests withdrawal of the rejection of claims 1-2, 4-7, 9-16, 18-25, 27-34, 37-46, 48-49, 56-71 under 35 U.S.C. 112 as lacking enablement.

(ii) Written Description

Examiner alleges that claims 1-2, 4-7, 9-16, 18-25, 27-34, 37-46, 48-49, 56-71 are rejected under U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses Examiner's rejection.

Applicant submits that possession of an invention is not limited to a description of actual reduction to practice. Possession of a claimed invention may be shown by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. The specificity of disclosure necessary to satisfy the written description requirement depends on the level of skill and knowledge in the art.

In the present case, the amino acid sequences of numerous Family 11 xylanases are disclosed in Figure 1 and the sequence listing. As discussed in relation to enablement, alignment of the sequences shows that certain amino acids in the sequence are conserved. Equipped with the amino acid sequences disclosed in Figure 1, it would be a simple matter for a person of skill in the art to produce a modified Family 11 xylanase comprising one or more of the substituted amino acids recited in claim 1 by employing well-known recombinant techniques such as plasmid preparation, restriction enzyme digestion, polymerase chain reaction, oligonucleotide phosphorylation, ligation, transformation and DNA hybridization (see page 26, lines 1-5). Thus, the broad disclosure of the Family 11 amino acid sequences and which amino acids are conserved,

coupled with the ease in which a person of skill in the art could prepare a modified xylanase, makes it clear that the invention is described with sufficient specificity to convey that the Applicant invented the subject matter of claim 1.

Examiner alleges that the genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of functions or no activity at all.

Amended claims 1 and 49 of the present application specify that the modified xylanases possess a common function, namely enhanced thermophilicity. Furthermore, as stated on page 15, paragraph 1 of the description, Family 11 xylanases exhibit significant amino acid sequence identity and similar molecular structure.

> Family 11 xylanases share extensive amino acid sequence similarity (Figure 1). Structural studies of several Family 11 xylanases indicate that Family 11 xylanases from bacterial and fungal origins share the same general molecular structure (U.S. 5,405,769; Arase et al 1993). In addition, most Family 11 xylanases identified so far exhibit three types of secondary structure, including beta-sheets, turns and a single alpha helix.

While it is true that, in unpredictable arts, adequate written description of a genus which embraces widely variant species generally may not be achieved by disclosing only one species, it also true that there may be situations where one species adequately supports a genus. As stated in the Revised Interim Guidelines, "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus in view of the species disclosed."

The Applicant was clearly in possession of the necessary common attributes possessed by members of the Family 11 genus. As evidenced from the Family 11 xylanase amino acid sequences set out in Figure 1, and the sequence listing, it is clear that

Family 11 xylanases do not exhibit widely variant properties, but rather exhibit similar molecular structure. Thus, it is submitted that the representative disclosures of the *Trichoderma reesei* xylanase II mutants is adequate. Accordingly, Applicant submits that the claims do not lack adequate written description support.

For these reasons, as stated above, Applicant requests withdrawal of the rejection of claims 1-2, 4-7, 9-16, 18-25, 27-34, 37-46, 48-49, 56-71 under 35 U.S.C. 112 as lacking written description support.

Claim Rejections – 35 USC 102

Examiner rejects claims 1-2, 4-7, 9-16, 18-25, 27-34, 37-46, 48, 56-71 under U.S.C. 102(e) as being anticipated by NRC of Canada (NRC) et al. (WO 01/92487 A2, Dec 6, 2001, filed in English, designating US, filed on 5-31-2001 with priority benefit to US 60/213,803, 5-31-2000) or Wing Sung (US20030166236 A1, published 9-4-03, with priority date 5-31-2000).

The Inventor (Wing L. Sung) and Applicant (National Research Council of Canada) for the present application are the same as those of the cited prior art documents. This can be seen on the face of the documents. Thus, Applicant submits that the prior PCT application, which designates the United States, and US20030166236 A1, were not filed "by another" as required under 35 USC 102(e).

It is clearly a requirement of both (1) and (2) of 102(e) that either an application or a patent must be "by another." Below is an excerpt from the MPEP that describes what is meant by "by another."

2136.04 Different Inventive Entity; Meaning of "By Another" [R-1]

IF THERE IS ANY DIFFERENCE IN THE INVENTIVE ENTITY, THE REFERENCE IS "BY ANOTHER"

"Another" means other than applicants, *In re Land*, 368 F.2d 866, 151 USPQ 621 (CCPA 1966), in other words, a different inventive entity. The inventive entity is different if not all inventors are the same. The fact that the application and reference have one or more inventors in common is immaterial. *Ex parte DesOrmeaux*, 25 USPQ2d 2040 (Bd. Pat. App. & Inter. 1992) (The examiner made a 35 U.S.C. 102(e) rejection based on an issued U.S. patent to three inventors. The rejected application was a continuation-in-part of the issued parent with an extra inventor. The Board found that the patent was "by another" and thus could be used in a 35 U.S.C. 102(e)/103 rejection of the application.).

A DIFFERENT INVENTIVE ENTITY IS *PRIMA FACIE* EVIDENCE THAT THE REFERENCE IS "BY ANOTHER"

As stated by the House and Senate reports on the bills enacting section 35 U.S.C. 102(e) as part of the 1952 Patent Act, this subsection of 102 codifies the Milburn rule of *Milburn v. Davis-Bournonville*, 270 U.S. 390 (1926). The Milburn rule authorized the use of a U.S. patent containing a disclosure of the invention as a reference against a later filed application as of the U.S. patent filing date. The existence of an earlier filed U.S. application containing the subject matter claimed in the application being examined indicates that applicant was not the first inventor. Therefore, a U.S. patent, ** a U.S. patent application publication or international application publication, by a different inventive entity, whether or not the application shares some inventors in common with the patent, is *prima facie* evidence that the invention was made "by another" as set forth in *> 35 U.S.C.< 102(e). *In re Mathews*, 408 F.2d 1393, 161 USPQ 276 (CCPA 1969); *In re Facius*, 408 F.2d 1396, 161 USPQ 294 (CCPA 1969); *Ex parte DesOrmeaux*, 25 USPQ2d 2040 (Bd. Pat. App. & Inter. 1992). See MPEP >§ 706.02(b) and< § 2136.05 for discussion of methods of overcoming > 35 U.S.C.< 102(e) rejections.

Thus, an application/patent cannot be properly cited under 102(e) unless it is by another. Since the inventors on this application and the inventors/authors of the cited documents are the same, i.e., the same inventive entity, the cited documents are not

properly cited under section 102(e). Accordingly, Applicant requests removal of the rejection under U.S.C 102(e).

Double Patenting

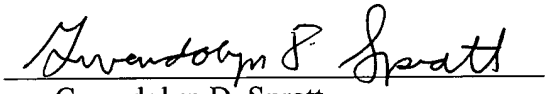
Examiner rejects claims 1, 2, 4-5 and 6 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 6 of U.S. Application No. 10/307,441.

Applicants note, initially, that this rejection should be recited as a "provisional" obviousness-type double patenting rejection as neither the cited application nor the present application has been indicated to have allowable claims. Furthermore, U.S. Application No. 10/307,441 is abandoned. A divisional of Application No. 10/307,441 ('441) was filed on March 17, 2006 (serial number not yet available). Applicant will submit a terminal disclaimer in compliance with 37 CFR 1.321(c) with respect to the commonly owned divisional patent application of Application No. '441 when there has been an indication of allowable subject matter.

It is respectfully submitted that the above-identified application is now in a condition for allowance and favorable reconsideration and prompt allowance of these claims is respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, the Examiner is invited to contact the Applicant's undersigned attorney at the telephone number listed below.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $1,020.00 for the filing of a three month extension of time is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

By 
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Dated: August 8, 2006

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